



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁵ : B67D 5/58	A1	(11) International Publication Number: WO 92/09523 (43) International Publication Date: 11 June 1992 (11.06.92)
<p>(21) International Application Number: PCT/US90/07029</p> <p>(22) International Filing Date: 30 November 1990 (30.11.90)</p> <p>(60) Parent Application or Grant (63) Related by Continuation US 360,041 (CIP) Filed on 1 June 1989 (01.06.89)</p> <p>(71) Applicants (for all designated States except US): PALL CORPORATION [US/US]; 30 Sea Cliff Avenue, Glen Cove, NY 11542 (US). MERCK & CO., INC. [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065 (US).</p> <p>(72) Inventors; and (75) Inventors/Applicants (for US only) : MATKOVICH, Vlado, I. [US/US]; 11 Old Estate Road, Glen Cove, NY 11542 (US). SCHLAUCHDECKER, Thomas, E. [US/US]; 55 Stratton Drive, Hamilton Square, NJ 08690 (US). HENLEY, MARTIN, W. [US/US]; 4418 Lower Mountain Road, New Hope, PA 18939 (US). BORMANN, Thomas [US/US]; 2365 Willoughby Avenue, Seaford, NY 11783 (US).</p>		<p>(74) Agent: ROSE, Herbert, C.; Leydig, Voit & Mayer, 700 Thirteenth Street, N.W., Suite 300, Washington, DC 20002 (US).</p> <p>(81) Designated States: AT (European patent), AU, BE (European patent), BF (OAPI patent), BJ (OAPI patent), BR, CA, CF (OAPI patent), CG (OAPI patent), CH (European patent), CM (OAPI patent), DE (European patent), DK (European patent), ES (European patent), FI, FR (European patent), GA (OAPI patent), GB, GB (European patent), GR (European patent), HU, IT (European patent), JP, KP, KR, LU (European patent), ML (OAPI patent), MR (OAPI patent), NL (European patent), NO, SE (European patent), SN (OAPI patent), SU⁺, TD (OAPI patent), TG (OAPI patent), US.</p> <p>Published <i>With international search report.</i></p>
<p>(54) Title: CONTAMINATION-RESISTANT DISPENSING AND METERING DEVICE</p> <p>(57) Abstract</p> <p>This invention relates to the field of liquid dispensing and metering devices that dispense a solution in drop form and protects the solution from contamination. In applications where contamination and proper dosage is a concern, the prior art discloses dispensers related both to the use of anti-bacterial agents added to the solution to prevent contamination and the use of a single dose device. Both present problems, as the addition of the agent causes allergic reactions in some users, while the single dose device is inconvenient to the frequent user. Prior art dispensers also do not permit control of metering for proper dosage. This invention solves these problems by providing a filter in the dropper portion of the device to prevent contamination of the solution. The device includes a dropper (2) having an outlet (3) and filter (4). The filter is a composite consisting of a liquophilic component (5) and a liquophobic component (6).</p> <div data-bbox="860 1092 1461 1932"> </div>		

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**CONTAMINATION-RESISTANT
DISPENSING AND METERING DEVICE**

This application is a continuation-in-part application of United States Patent Application
5 Serial No. 07/360,041 filed June 1, 1989.

Technical Field

10 This invention relates to a liquid dispensing and metering device that is especially useful in, for example, the dispensing of optical drugs that typically need to be dispensed in drop form. The present invention provides such a device that also protects the solution from contamination while retained in the device.

Background of the Invention

15 This invention has wide application in situations where a liquid is required to be dispensed in metered amounts at regular intervals from a container and in which it is critical that contamination from outside, whether particulate or bacterial
20 in nature, be excluded. By "metering" is meant precise control or regulation of flow rate. Such a situation is most frequently encountered in the context of the dispensing of medicines such as oph-

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thalmic medicines but the utility of the invention extends to the dispensation and to the protection of any liquid against particulate contamination. For ease of understanding, however, the invention will
5 be described primarily in the context of the application that, as is presently anticipated, will be the most commercially attractive.

Many drugs, particularly those used in treatment of various eye disorders, are administered in
10 drop form. The drops are intended to free-fall onto the eye surface, where they distribute across the exposed eye. Dosage of these ophthalmic drugs is often crucial: lower than prescribed levels can result in failure of the treatment and consequent
15 progression of the disease, higher levels can result in untoward side effects that can also interfere with successful resolution.

Complicating the administration of these drugs is the fact that they are often required several
20 times a day and thus, to be practical, must be applied by the patients themselves and not by medical personnel who are formally trained in drug delivery. Patient administration of such drugs has resulted in two serious problems which must be solved for these
25 medications to be successfully used: container contamination and flow rate.

Container Contamination

The possibility that bacterial contamination may enter the drug container and proliferate there
30 is an ever-present problem that can destroy the utility of the medicine. This can be the result of dropper contact with a non-sterile surface, such as a body part, or by some other mechanism.

The problem can be most readily understood in

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the context of the administration of drops of an ophthalmic medicine. Ideally, the pendant drop formed at the tip of the conventional dropper container when the container is squeezed should be allowed to free-fall to the surface of the eye. In addition, the distance between the dropper tip and the surface of the eye should be kept reasonably close. This is important so that the momentum acquired by the free-falling drop will not be so great as to encourage the drop to splatter on impact with the eye surface and thus be substantially lost to the outer surface of the lids and face. Where administration is by a trained professional, it is relatively easy to ensure that the free-falling drop is discharged close to the eye surface. It is substantially more difficult to do this when the drug is self-administered. Gauging such short distances is physiologically difficult due to the inability to focus, and in addition the anticipation of the impacting drop often causes a blink and subsequent loss of portions of the drop. As a result, the user may inadvertently permit the dropper tip to contact the eye surface.

In any event, small amounts of eye liquids can thus be inadvertently permitted to commingle with the liquid of the drop to be delivered. Thus, when the pressure on the delivery container forcing the drop out is relieved, a small amount of the mixed liquids may be drawn back into the container. With time the bacteria originally present in the eye, both normal and pathological, will be permitted access to a medium which may cause them to proliferate. Thus, subsequent drops of medication may reintroduce to the eye either excessive levels of typically present bacteria, or large numbers of

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pathogens. Neither situation is acceptable.

To cope with the problems of contamination, drug manufacturers often introduce an anti-bacterial agent to the drug container. In most cases, this agent or preservative can be very effective at suppressing the growth of bacterial contaminants within the container. Unfortunately, there exists a significant population of patients for whom these preservatives represent ocular irritants, or in more severe cases, cause allergic reactions. Such untoward ocular reactions prevent such patients from using the drug in this kind of packaging. For these patients, single-use, non-preserved drug packaging is a partial answer, but at significantly increased cost and inconvenience.

Of course, similar problems are encountered with other drop-administered medicines, for example, for the ear or nose.

Container contamination can also be the result of particulate matter being drawn back into the container with the liquid in the dropper tip that has not been delivered as a drop. Over several drop deliveries in, for example, dusty conditions, a significant accumulation of dust in the container is possible. If the liquid to be delivered needs to be ultrapure as, for example, in certain microelectronic applications, such accumulation could raise a serious problem.

Flow Rate

Dosage of drugs administered as drops is regulated on the basis of the number of drops to be applied. Formation of the drops is directly related to flow rate or metering of the liquid from the container. The drops themselves fall from the dropper

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tip when the weight of the pendant drop exceeds the surface tension forces holding the drop to the dropper tip. In the ideal case, each drop should be identical to the previous one. In practice, however, other factors intervene to cause significant variation in drop size. One of the most significant factors is the rate of drop formation. Some attempts to control drop size and uniformity by precise control in manufacturing of tolerances of the dropper tip orifice have been somewhat successful. However, such controls are difficult to achieve and increase manufacturing costs. Furthermore, in using such devices, if the drop is formed rapidly, more liquid can be "injected" into the body of the drop as it is beginning to break free. These drops will be larger, and thus will carry more drug, than if the container is squeezed very slowly. In extreme circumstances, drug may be ejected in a steady stream, which renders control of dosage impossible.

While this is a minimal problem when the drugs are delivered by a trained professional, it becomes significant when the drugs are delivered by the patients themselves. The flow rate, which is directly related to the finger pressure while squeezing, cannot be easily controlled. The visual clue, that is, the growth of the drop itself, cannot be readily observed if the eye is about to receive the same drop or if the dropper is not positioned in the line of sight in use.

The problem of delivery control is not restricted to ophthalmic drugs, of course, and there is a clear need for controllable addition devices in a wide range of, for example, pharmaceutical dispensing applications.

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Description of the Invention

In the metering device defined in the present invention there is an inherently greater resistance to liquid flow than in a metering device of the prior art. For this reason, it becomes most difficult to produce a continuous stream of liquid by squeezing the container. This resistance to liquid flow also tends to damp out the natural variations in squeezing force that occur from moment to moment during use of a metering device of this type. As a result, the sequential drops metered from such a device tend to have a much more uniform size.

It is therefore an object of this invention to provide a flow metering device in which the problems of contamination and uncontrolled flow rate are substantially reduced.

It is a further object of this invention to provide a dropper for ocular medicines that is protected from inadvertent bacterial contamination and thus permit a significant reduction or the complete elimination of preservatives in the medicine.

It is another object of the invention to provide a liquid metering and dispensing device in which a liquid, such as a medicine, is dispensed as substantially uniform drops.

The above objects are provided by a device for dispensing a liquid in drop form which comprises a container having a dropper tip including a passageway for ingress of air to and egress of liquid from the device, the passageway communicating between the body of the container and an orifice, means for temporarily reducing the volume of the container and, disposed within the dropper tip, across, so as to intersect the passageway, and preferably adjacent

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the orifice thereof, a microporous membrane with pores of a size to resist the passage of undesired contamination, the membrane having a liquophilic portion permitting delivery of metered drops of a liquid to a desired location outside the container, and a liquophobic portion adapted to resist the passage of such liquid but to permit the passage therethrough of air, the passageway communicating with both the liquophilic and liquophobic portions of the membrane.

The membrane is sealed to the inside surface of the dropper within the tip region so as to prevent the passage of liquid around, as opposed to through, the membrane.

The membrane comprises two components in side-by-side or juxtaposed relationship. One component has a liquophobic character, that is, it resists the passage of liquids. The other component has a liquophilic character, that is, liquids pass through it readily. Thus, liquids exiting the container through the porous membrane will pass exclusively through the liquophilic component and will be rejected by the liquophobic component. Liquids being sucked back into the container will pass exclusively through the liquophilic component. However, air will flow into the container to replace the expelled liquid, through the liquophobic side, displacing any liquid adhering to the walls of the passageway and causing the liquid to flow through the membrane and into the reservoir of the container.

The Container

In use, the container functions as a reservoir for the liquid to be dispensed. It is provided with means to temporarily reduce its volume, typically by

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providing that at least part of the container is elastically deformable. Thus, pressure on a deformable portion of the container will reduce the effective volume and force the liquid contained therein
5 out of the container when it is appropriately oriented.

After a desired number of drops have been expelled from the container and the deforming pressure is removed, the liquid below the membrane in the tip
10 is drawn back into the container. It is preferred that this occurs as a continuous column, that is, no droplets should break away and be left behind in the tip area. Such droplets could be a hospitable environment for bacterial growth and as such should be
15 avoided so far as possible. Making the passageway narrow helps to maintain a continuous column. Also, appropriate selection of the material from which the wall of the passageway is formed, so as to have a critical wetting surface tension matched to the surface
20 tension of the liquid employed, enhances draining from the passageway as a continuous column. Making the volume of the tip area very small helps to minimize the problem of retained drops, generally. It is, therefore, particularly preferred
25 that the volume between the orifice of the dropper and the surface of the composite membrane be as small as possible. In particular, the volume of the tip of the dispenser (i.e., between the orifice and the membrane) is of a volume which is sufficiently
30 small to ensure that all of the liquid flows back to the membrane without air percolating past liquid in the tip. Volumes of the order of from about 0.001 to about 0.15 cm³ are suitable and most preferred are volumes of from about 0.05 to about 0.1 cm³.

35 The tip area of the dropper can be designed to

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provide membrane support by various means including, for example, a series of ribs on the inside surface of the dropper tip and/or an interior beading providing a seating surface to which the membrane can be bonded. Care should, however, be exercised to ensure that such support devices do not impede or distort the flow of metered drops from the device. Support could also be provided by the provision of a transverse septum or bar that would help resist any tendency of the membrane to deform under pressure.

Wetting of Porous Media

The wettability or liquophilicity of a porous structure, e.g., a membrane, is a function of that structure's critical wetting surface tension (CWST) (discussed below) and the surface tension of the applied liquid. If the CWST is at least as high as the surface tension of the liquid, the liquid will spontaneously wet the porous structure, which may be termed "liquophilic" with respect to that liquid. Conversely, if the CWST is lower than the surface tension of the liquid then it will not be wet and will be liquophobic with respect to that liquid.

When a liquid is brought into contact with the upstream surface of a porous medium and a small pressure differential is applied, flow into and through the porous medium may or may not occur. A condition in which no flow occurs is that in which the liquid does not wet the material of which the porous structure is made.

A series of liquids can be prepared, each with a surface tension about 3 dynes/cm higher compared with the one preceding. A drop of each may then be placed on a porous surface and observed to determine whether it is absorbed quickly, or remains on the

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surface. For example, applying this technique to a 0.2 μm porous polytetrafluoroethylene (PTFE) membrane, instant wetting is observed for a liquid with a surface tension of about 26 dynes/cm. However, the structure remains unwetted when a liquid with a surface tension of about 29 dynes/cm is applied.

Similar behavior is observed for porous media made using other synthetic resins, with the wet/unwet values dependent principally on the surface characteristics of the material from which the porous medium is made and, secondarily, on the pore size characteristics of the porous medium. For example, fibrous polyester, specifically polybutylene terephthalate (hereinafter "PBT") sheets which have pore diameters less than about 20 μm will be wetted by a liquid with a surface tension of about 50 dynes/cm, but will not be wetted by a liquid with a surface tension of about 54 dynes/cm.

In order to characterize this behavior of a porous membrane, the term "critical wetting surface tension" (CWST) is defined as follows. The CWST of a porous medium may be determined by individually applying to its surface a series of liquids with surface tensions varying by about 2 to about 4 dynes/cm, and observing the absorption or non-absorption of each liquid. The CWST of a porous medium, in units of dynes/cm, is defined as the mean value of the surface tension of the liquid which is absorbed and that of a liquid of neighboring surface tension which is not absorbed. Thus, in the examples of the two preceding paragraphs, the CWST's are about 27.5 and about 52 dynes/cm, respectively.

In measuring CWST, a series of standard liquids for testing is prepared with surface tensions varying in a sequential manner by about 2 to about

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4 dynes/cm. Ten drops from each of at least two of the sequential surface tension standard liquids are independently placed on representative portions of the porous medium and allowed to stand for 10 minutes. Visual observation is made after 10 minutes. Wetting is defined as absorption into the porous medium by at least nine of the ten drops within 10 minutes. Non-wetting is defined by non-absorption or non-wetting of at least nine of the ten drops in 10 minutes. Testing is continued using liquids of successively higher or lower surface tension, until a pair has been identified, one wetting and one non-wetting, which are the most closely spaced in surface tension. The CWST is then within that range and, for convenience, the average of the two surface tensions is used as a single number to specify the CWST.

A number of alternative methods for contacting porous media with liquids of sequentially varying surface tension can be expected to suggest themselves to a person knowledgeable of physical chemistry after reading the description above. One such involves floating a specimen on the surfaces of liquids of sequentially varying surface tension values, and observing for wet-through of the liquid or, if the fiber used is more dense than water, observing for sinking or floating. Another means would clamp the test specimen in a suitable jig, followed by wetting with the test liquids while applying varying degrees of vacuum to the underside of the specimen.

Appropriate solutions with varying surface tension can be prepared in a variety of ways; however, those used in the development of the product described herein were:

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	<u>Solution or fluid</u>	<u>Surface Tension range, dynes/cm</u>
	Sodium hydroxide in water	94 - 110
	Calcium chloride in water	90 - 94
5	Sodium nitrate in water	75 - 87
	Pure water	72.4
	Acetic acid in water	38 - 69
	Ethanol in water	22 - 35
	n-Hexane	18.4
10	FC77 (3M Corp.)	15
	FC84 (3M Corp.)	13

Liquophilic Medium

Suitable materials for the liquophilic medium include forms of polyamides, polyvinylidene fluoride or difluoride (PVDF), and cellulose compounds, such as nitrocellulose and mixed esters of cellulose, as well as glass fiber mats with suitable binders. Hydrophilic, microporous polyamide membranes, particularly nylon 66 membranes, and PVDF membranes are especially preferred.

A preferred microporous, hydrophilic nylon 66 membrane material having high binding capacity, uniformity, controlled pore size, and high surface area is Biodyne™, available from Pall Corporation or one of the hydrophilic membranes described in U.S. Patent 4,340,479, the subject matter of which is specifically incorporated herein. This patent describes a polyamide resin, a microporous, hydrophilic membrane formed from the resin, and a method of forming the membrane. The membrane is a skinless alcohol-insoluble polyamide membrane having a ratio of $\text{CH}_2:\text{NHCO}$ of methylene CH_2 to amide NHCO groups within a range of about 5:1 to about 7:1 and

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has pores that are substantially uniform from surface to surface and a particle removal rating of about 0.1 μM to about 5 μM .

Another preferred membrane useful as the liquophilic medium is the CARBOXYDYNE® membrane, also available from Pall Corporation. CARBOXYDYNE® is a hydrophilic, microporous, skinless nylon 66 membrane with controlled surface properties formed by the co-casting process described in U.S. Patent 4,707,266, also specifically incorporated herein. As discussed below, the process involves cocasting a polyamide, such as the type described in U.S. Patent 4,340,479, preferably nylon 66, and a polymer containing an abundance of ionizable acidic groups, such as carboxyl groups, to form a membrane having controlled surface properties characterized by carboxyl functional groups at its surface. Besides being hydrophilic, these membranes have pore sizes from about 0.04 to about 10 micrometers or more and in certain instances have modified zeta potentials (e.g., negative zeta potentials in acidic media). They also have filtration efficiencies ranging from molecular dimensions (pyrogens) to particulates larger than the pore sizes.

Yet another preferred membrane useful as a medium for the liquophilic compound of the present invention is the Posidyne® membrane, also available from Pall Corporation. Posidyne® is a polyamide membrane which is similar to Carboxydyne® and the media described in U.S. Patent 4,707,266, in both chemical and physical properties as well as in its method of manufacture. This and similar materials are described in U.S. Patent 4,702,840, specifically incorporated herein by reference. While these materials are surface-modified, hydrophilic,

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microporous, polyamide membranes, like those described in U.S. Patent 4,707,266, they are charge-modified to have strongly positive zeta potentials in alkaline media rather than negative zeta potentials. This results from the cationic, water-soluble, quaternary ammonium, thermosetting polymers with which the polyamide resin is cocast during its manufacture. As the surface- and charge-modifying polymers, epoxy-functional polyamido/polyamino epichlorohydrin resins are preferred.

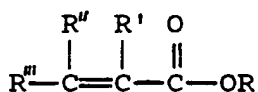
These hydrophilic, microporous, substantially alcohol-insoluble polyamide membranes with controlled surface properties are formed by cocasting an alcohol-insoluble polyamide resin with a water-soluble, membrane-surface-modifying polymer having functional polar groups. Like the preferred hydrophilic, microporous nylon membranes which do not have controlled surface modified polar groups present, the polyamide membranes of the present invention having controlled surface properties are also skinless; that is, they are characterized by through pores extending from surface to surface which are of substantially uniform size and shape.

Polyvinylidene fluoride membranes are not inherently water-wettable but can be rendered such by an appropriate surface modification. Terms such as "surface," "polymeric substrate surface," "membrane surface," or like terms, used in the singular or plural, are intended herein to include not only the gross surfaces, i.e., the external or outer surfaces, such as those which are exposed to view, but also the internal surfaces or those surfaces which define the pores of the polymeric substrate or medium, that is, the substrate or membrane surface is that portion of the polymeric substrate or membrane

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medium which is capable during use of being contacted by a fluid, particularly a liquid. The term "surface modification", or like terms, as used in describing surface-modified PVDF membranes, refers specifically to changes in the "surface," described above, wherein chemical bonds are formed between the surface of the polymer being modified and suitable compound or compounds used to modify the polymer surface, rendering said surface modifications permanent, non-removable, and non-leachable. Microporous, polyvinylidene fluoride membranes which have been surface modified to render them hydrophilic are commercially available. An example of a suitable material is described by Joffee et al. in U.S. Patent 4,774,132, "Polyvinylidene Difluoride Structure," assigned to Pall Corporation, and by Gsell et al. in a pending application, U.S. Serial No. 07/447,415, "Filtration Media With Low Protein Adsorbability," both specifically incorporated herein by reference.

The membranes described in U.S. Patent 4,774,132 include microporous PVDF membranes which are surface-modified by having grafted thereto a polymer derived at least in part from polymerizable vinylic monomer, the modifying polymer including functional groups sufficiently polar or ionic to provide the membrane with a critical surface energy of at least about 80 dynes/cm. The polymerizable vinylic monomer preferably includes at least one carboxyl group, preferably conjugated with an ethylenically unsaturated bond. Most preferably the polymerizable vinylic monomer has the general formula:



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wherein R is H, an aminoalkyl or quaternized aminoalkyl group having 1 to 3 carbon atoms, or a hydroxyalkyl group having 1 to 3 carbon atoms; R', R'', and R''' independently are H, an alkyl group having 1 to 3 carbon atoms, a carboxyl group, a carboxyalkyl group having 1 to 3 carbon atoms, or a hydroxyalkoxycarbonyl group having 1 to 3 carbon atoms.

The method of making these membranes involves the steps of contacting a PVDF medium with an alkali solution, such as a potassium hydroxide solution, to form activated sites on the surface of the medium. The activated structure is then rinsed to remove residual alkali and subsequently contacted with a solution of a polymerization initiator, such as potassium peroxydisulfate, and the polymerizable vinylic monomer. The monomer is then polymerized and grafted to the surface of the medium.

Gsell et al describe a porous polymeric PVDF medium having a low affinity for amide group-containing materials formed from a PVDF substrate and a surface-modifying polymeric material having a low affinity for amide group-containing materials formed in situ at and covalently bonded to the surface of the PVDF substrate. The surface-modifying polymeric material is derived from a monofunctional monomer, preferably unsaturated, which has at least one hydroxyl group, for example, hydroxyalkyl acrylates and methacrylates.

As discussed above, wettability or liquophilicity is a function of the CWST of the porous membrane and the surface tension of the liquid. Wettability may also be expressed in terms of intrusion pressure required for liquid to penetrate into the pores of the membrane. Membrane materials which are partic-

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ularly preferred have intrusion pressures of, or close to, zero for the liquids with which they are used.

Liquophobic Medium

5 The term "liquophobic" as used herein is effectively the obverse of the term "liquophilic", that is, a porous liquophobic material has a CWST lower than the surface tension of the applied liquid and is not readily or spontaneously wetted by the applied liquid(s). Liquophobic materials are characterized, then, by a high contact angle between a drop of liquid placed on the surface and the surface. Such a high contact angle indicates poor wetting.

15 Another way of expressing the suitability of a material for use as the liquophobic component of the instant invention relates to the wetting resistance characteristics of the material. A suitable material should be capable of resisting a liquid intrusion pressure greater than the pressure that can be generated by manual squeezing of the dispensing bottle.

25 Suitable materials include polyolefins, such as polypropylene, polyhalogenated polyolefins, particularly perfluorinated polyolefins, such as polytetrafluoroethylene, and polyvinylidene difluoride, as well as sulfones. Polytetrafluoroethylene is a preferred polymer and unmodified, as well as surface modified polyvinylidene difluoride, particularly a fluoropolymer-grafted microporous polyvinylidene difluoride membrane or similarly surface modified polyamides are most preferred. Methods of forming the fluoropolymer-grafted polyvinylidene difluoride as well as similarly surface modified polyamides are

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described by Degen et al. in U.S. Patent 4,954,256, "Hydrophobic Membranes", incorporated herein by reference. More particularly, the fluoropolymer grafted polymers may be formed by contacting a

5 microporous polymeric substrate or membrane with a solution of at least one polymerizable fluorine-containing monomer and exposing the membrane to ionizing radiation to produce a microporous hydrophobic polymeric membrane in which a

10 hydrophobic fluoropolymer is chemically bonded to all the surfaces of the microporous membrane substrate. The surface-modified membranes have CWST's of less than about 28 dynes/cm. Both polyamides and fluorine-containing polymers, such as

15 PVDF may be used as the substrate. The monomer contains an ethylenically unsaturated group and a fluoroalkyl group, the latter preferably being a perfluoroalkyl group.

The surface modifications described above for

20 enhancing or creating a membrane of reduced CWST, also, as described earlier, are permanent, non-removable, and non-leachable because the modifying polymers are chemically bound to the substrates which they modify. This is in contrast to the

25 conventional treatment of normally liquophilic membranes by addition of liquophobic agents to the membrane or a section of the membrane, such as silicone oils or like compounds, which coat the membrane surfaces but are not chemically bound

30 thereto, such as by covalent bonds. Such prior art surface treated membranes have the drawback that liquid contact with such treated surfaces can result in leaching of the liquophobic agents into the liquid to be delivered. There are several disadvantages to such leaching, including progressively

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reduced liquophobicity of the treated membrane and simultaneous contamination of the delivered liquid. Such contamination is of particular concern in drops delivered to the sensitive tissues of the eye.

5 The Composite Membrane

 The composite membrane used in the present invention has both a liquophilic, preferably hydrophilic, component and a liquophobic, preferably hydrophobic, component. Most frequently, the edges of these media will be bonded together along the line of contact so as to form a single unit with the components in side-by-side or abutting (as opposed to face-to-face) relationship to one another. Part of the composite will be liquophilic with respect to the liquid to be dispensed with the device and the other part will be liquophobic with respect to that same liquid.

 It is to be understood, however, that the term "composite membrane" is also intended to cover the functional equivalent of such a membrane where the two components are not physically joined but act to close off separate but adjacent exit passages from the device. One example would be provided by a device with a dropper tip having a transverse septum or bar in the area of the dropper tip dividing the exit passageway effectively in two. With such a device each membrane could be sealed to the septum or bar and the inside wall of the tip and there would be no need for bonding the two membranes together. Indeed, this configuration might confer useful support benefits for the membranes.

 The liquophilic and liquophobic membranes can be attached within the dropper tip by known techniques, such as heat welding or ultrasonic welding.

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For proper function the formation of a bacteria-tight seal at the entire perimeter of the weld is critical. It is also necessary to form a bacteria-tight seal at the junction of the liquophilic and
5 liquophobic membranes. This can be achieved by bonding the membranes together in a separate operation, with the minimum overlap required to assure a complete seal. Ultrasonic welding techniques are often preferred for this operation though good results can be obtained by heat sealing. Overlaps of
10 less than or equal to about 3 mm (0.12 in) are preferred, and less than or equal to about 1 mm (0.039 in) are most preferred.

After bonding the membranes, discs of the membrane pairs may be punched out using conventional
15 die punching techniques. The position of the die above and below the bond line can be used to set the relative proportion of the liquophilic and liquophobic portions of the membranes.

20 After punching, the discs may be transferred to the base of the dropper tip and welded in position. Alternatively, two separate regions of the dropper base may be defined and individual components of the liquophilic and liquophobic membranes welded
25 thereto.

It is found that the bonding operation is often much simplified if the substrate membrane of both the liquophilic and liquophobic components is formed from the same basic material. This can be achieved
30 by surface modification of chemically identical or closely related polymeric membranes to give liquophilic and liquophobic components which are then joined together to form the composite membranes useful in the device of the invention. Composite
35 membranes in which both components are suitably

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surface-modified polyamides are particularly preferred. Also, composite membranes formed from naturally hydrophobic polyvinylidene difluoride and its surface-modified counterpart are preferred.

5 The liquophobic component of the membrane of the present invention typically has a CWST of less than about 35 dynes/cm and typically from about 20 dynes/cm to about 30 dynes/cm. By contrast, the
10 liquophilic component of the membrane has a CWST of at least about 50 dynes/cm, such as from about 70 dynes/cm to about 100 dynes/cm, and preferably from about 72 dynes/cm to about 95 dynes/cm.

Both components of the membrane have a pore size adapted to resist passage of an undesired con-
15 taminant. Most frequently, in the medicinal context, this will be bacterial contamination. In this context, for the liquophilic component, pore sizes of from about 0.04 to about 0.65 μm are suitable. Preferred are pore sizes of from about 0.01 to about
20 0.45 μm and most preferred are pore sizes of from about 0.15 to about 0.2 μm . The liquophobic component, however, generally has a pore size of from about 0.01 to about 0.45 μm with from about 0.04 to about 0.2 μm preferred and from about 0.1 to about
25 0.2 μm most preferred. If particulate contamination is the main concern, the pore sizes can be redefined accordingly.

The surface area of the composite membrane can be divided between liquophilic and liquophobic com-
30 ponents in any convenient proportion. However, the proportions should be consistent with the functions that the components have to fulfill. The liquo-philic membrane should be of such a size that the liquid within the container will be dispensed in
35 drops at an appropriate rate. Too large an area

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could result in a high rate of flow or even, in extreme cases, a stream of liquid. On the other hand, too small an area would result in a very low drop delivery rate.

5 It is preferred that the liquophilic and liquophobic components of the composite membrane be formed from the same polymeric material, the surface of the polymeric material of at least one of the components being permanently chemically modified.
10 Thus, a material which is inherently either liquophilic or liquophobic toward a particular solvent is permanently, chemically surface-modified to provide the material for the other of the liquophobic or liquophilic medium. Examples of
15 particular combinations of such liquophilic and liquophobic components suitable as the composite membranes, in the order of preference, are the following:

20 a hydrophilic polyamide, such as Biodyne™, and a surface-modified hydrophobic polyamide, such as that described in U.S. Patent 4,954,256;

 a hydrophilic polyamide, such as Posidyne®, and a surface-modified hydrophobic polyamide, such as that described in U.S. Patent
25 4,954,256;

 a hydrophilic polyamide, such as Carboxydyne®, and a surface-modified hydrophobic polyamide, such as that described in U.S. Patent
30 4,954,256;

 a PVDF membrane, surface-modified to render it hydrophilic, such as that described in U.S. Patent 4,774,132 and an unmodified hydrophobic PVDF;

 and a PVDF membrane, surface-modified to
35 render it more hydrophobic (i.e. having a lower

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CWST), such as the material described in U.S. Patent 4,954,256.

Metering Function of the Hydrophilic Component

An important aspect of the present invention is the provision of a deformable dropper bottle that meters out drops at a carefully regulated flow rate. The metering effect, i.e., the control of flow rate and uniformity of drop size, is determined by two factors: the pore size and, as indicated above, the area, specifically the gross surface area. When the liquophilic portion of the membrane selected is hydrophilic with respect to the liquid (i.e., water) to be dispensed and has a porosity that is fine enough to exclude bacteria, the factor that most affects the rate at which drops are dispensed is the gross surface area (i.e., the external or outer surfaces, such as those exposed to view) of the liquophilic, preferably hydrophilic, portion of the membrane. Thus, drop formation rate is largely independent of the pressure differentials caused by any deformations of the dropper bottle likely to be encountered in the normal use of such devices. This is, of course, a significant safety factor since the dropper bottle, by design and intent, will be for use by medically untrained people with varying interpretations of the level of pressure needed to express one drop from the bottle.

The liquophilic, preferably hydrophilic, membrane surface area that is best suited to produce an appropriate liquid flow rate in the above circumstances is found to be about from about 20 mm² to about 90 mm², and preferably from about 40 mm² to about 50 mm².

The liquophobic, preferably hydrophobic, com-

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ponent should be large enough to accommodate relatively easy but controlled access of air to replace the liquid dispensed. It is found that, with devices of the size normally employed for eye drop-
5 pers, satisfactory results may be obtained when the proportion of the liquophilic component is from about 50 to about 70% of the total gross surface area of the composite membrane. This provides sufficient surface area of the liquophilic, preferably
10 hydrophilic, component to ensure a satisfactory flow rate from the dropper bottle when it is deformed. Particularly preferred, however, are membranes where about 60 to about 70% of the gross surface area is provided by the liquophilic component. It is recog-
15 nized, however, that some applications may require proportions outside the above ranges.

Description of the Drawings

Figure 1 is a diagrammatic cross-section of the tip and adjacent portions of a deformable container
20 according to the invention.

Figure 2 is a plan view of the microporous membrane shown separate from the container.

Description of Preferred Embodiments

The invention is further described with specific reference to the drawings which illustrate a preferred embodiment of the invention. In the drawings, Figure 1 represents a partial cross-section of a dropper according to the invention. Figure 2 represents a plan view of a composite membrane according to the invention.
25
30

In Figure 1, a container (partially shown in

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dotted outline as 1) has a dropper tip portion or a cap 2 which includes a passageway 7 that extends from the upstream or inlet side of a dispensing cap (or outlet end of the container body where the tip portion and container body are of unitary construction) and which terminates in an orifice 3. Disposed in the dropper tip 2, across and intersecting the passageway 7 adjacent the container is a membrane 4 sealed to the surface of the dropper tip 2. The membrane 4 has a generally circular configuration conforming to the dimensions of the opening in the dropper tip 2. The membrane 4 is a composite of two components in side-by-side relationship: a liquophilic component 5 and a liquophobic component 6 sealed at their line of contact to form a unitary disc-shaped composite membrane. In use, the container is inverted, that is to say, placed with its dropper tip downwards, and squeezed. This reduces the effective volume of the container and creates a pressure differential between the inside and the outside of the container such that the liquid contained therein is expelled. The liquid is typically a drug in an aqueous solution intended for treatment of eye disorders. The drug solution wets and then passes through the liquophilic membrane into the dropper tip. As the pressure is maintained, the liquid emerges from the dropper tip orifice and begins to form a pendant drop. When used for administering ocular medicine, it is intended that this drop fall into the eye of the patient. As the drop reaches critical size, it breaks away from the dropper tip orifice and falls into the eye. When the squeezing pressure on the container is removed, a differential pressure is created between the outside of the container and the

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inside, as the elastic walls of the container attempt to return to their original shape. This differential pressure causes the liquid remaining in the dropper tip to be drawn back towards the inside of the container. In doing so, the liquid must pass through the liquophilic component of the membrane. The dropper tip is designed so that substantially all if not all of the liquid remaining after the drop is dispensed is drawn back into the container. As the retreating liquid/air interface in the dropper tip reaches the liquophilic membrane, flow through the liquophilic membrane halts. This is because significantly higher pressure than is available from recovery of the elastically deformed walls of the container, which reverses the pressure differential referred to above, is required to drive air through the wetted liquophilic membrane. Incoming air, however, is necessary to compensate for the volume of the drug dispensed. This can enter the container through the adjacent liquophobic membrane. Thus, sufficient air will enter the container via the liquophobic membrane to equalize the pressure inside and out.

In the event that the liquid in the dropper tip has become contaminated, for example, by contact with bacteria from the patient's optical fluids, the bacterial component is filtered by the liquophilic component as the rest of the liquid is drawn back into the container. Thus, liquid and air re-entering the container from the dropper tip area are filtered free of bacterial contamination.

Since the internal volume and shape of the dropper tip are selected to minimize the possibility of any retained liquid, any bacteria present and trapped on the liquophilic and liquophobic membrane

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components are thus exposed to the air. Such exposure may inhibit growth such that subsequent drops dispensed from the container will be either free or substantially free of contaminants previously entrained in the dropper tip. Thus, the tip will be returned substantially to its pre-contamination state with each cycle of use. If contamination is likely to have occurred and it is imperative that no amount of bacteria be returned to the eye, then the first drop or drops of drug may be discarded so as to purge the tip. Experiments in which the dropper has been seeded with known levels of bacteria suggest that this procedure is effective.

Experimental Data

To test the concept, two dropper bottles and tips were constructed using a 0.2 μm rated Biodyne[®] nylon 66 membrane as the liquophilic segment, and 0.02 μm rated polytetrafluoroethylene membrane as the liquophobic segment. The membranes were first bonded together along their midlines using a Branson ultrasonic welder with a gold booster and a flat 2" x 2" welding horn. An approximately 1 to 3 mm overlap was formed at the weld line. The dropper tips were modified by filling the excess space between the membrane and the tip with an epoxy compound, resulting in a volume of approximately 0.1 cm^3 . Discs were then cut from the resulting composite strip and ultrasonically welded at their perimeters to the base of the dropper tips. In these tips approximately 60% of the total membrane area was occupied by the liquophilic membrane.

The tips were then aseptically inserted into dropper bottles containing an ophthalmic drug timolol maleate, but with no preservatives included.

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A solution containing approximately 1×10^5 per milliliter of p. auriginosa was prepared. Bottle 1 was oriented tip upright, squeezed, and held. Then, an aliquot of 100 μ l of the p. auriginosa solution was injected into the opening of the dropper tip using a microsyringe. The pressure on the bottle was then released, and the 100 μ l aliquot was observed to draw back into the bottle. The second bottle, bottle C, did not have any bacteria solution injected and was kept as a control.

Ten minutes after the inoculation of bottle 1, a sequence of 4 drops of timolol maleate was squeezed out and each drop directed to fall into a quadrant of an agar plate (Q1 to Q4). Each drop was then spread by streaking across the quadrant with a sterile loop. One day later, the same procedure was repeated with another agar plate. This repetitive sampling was continued for 14 days. In parallel, the control bottle, bottle C, was sampled in the identical manner.

The data for the inoculated bottle, bottle 1, is shown below:

		<u>COLONIES/QUADRANT</u>			
	<u>DAY</u>	<u>Q1</u>	<u>Q2</u>	<u>Q3</u>	<u>Q4</u>
25	10 min	128	90	65	51
	1st	0	0	0	0
	2nd	0	0	0	0
	3rd	0	120 ^a	0	0
	4th to 14th	0	0	0	0

^a Note: colonies seen were not p. aeuroginosa.

The control bottle, bottle C, had zero counts for all days in all quadrants.

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In this experiment, the 100 μ l inoculation was observed to be drawn back into the bottle. Thus, the bacteria in the aliquot was presented to the composite membrane at the base of the dropper tip.

- 5 Lack of p. aeuriginosa growth in the samples from days 1 to 14 demonstrates that none of the bacterial challenge reached the contents of the bottle.

- The data from the 4 drop sequence taken 10 minutes after inoculation is a confirmation that p. aeuriginosa bacteria was present in the dropper tip and, in addition, that it would not flourish or could be purged by the removal of several drops.
- 10

- In the discussion of the preferred embodiment illustrated in the drawings, a device adapted to dispense ocular medicine was taken as the paradigm. It is to be understood, however, that the device of the invention could be used for other purposes in which it is convenient to dispense the medicine in the form of drops such as, for example, medicine for the ears or the nose. In general, the medicine will be made up in an aqueous or saline solution; thus the terms liquophilic and liquophobic will most conveniently imply hydrophilic and hydrophobic, respectively. It is understood, however, that occasionally medicines are made up in a light oil and thus the broadest interpretation of liquophobic and liquophilic must embrace the use of such liquids as media for the application of the medicine.
- 15
- 20
- 25

- The body of the container is provided with means for temporarily reducing the volume of the container. Typically, this will be by providing that at least part of the walls of the container are elastically deformable. Thus, squeezing the container will temporarily reduce its volume. Alternative means such as a movable plunger or an inflat-
- 30
- 35

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able insert in the container could be devised but are not generally preferred over the simplicity of the squeezable container.

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Claims:

1. A device for dispensing liquids in drop form which comprises a container having a dropper tip including a passageway for ingress of air to and egress of liquid from said device, said passageway communicating between the container and an orifice in the dropper tip; means for temporarily reducing the volume of the container; and a microporous composite membrane with pores of a size to resist passage of contaminants, said membrane having a liquophilic component permitting delivery of drops of a liquid to a desired location outside the container and a liquophobic component adapted to resist the passage of such liquid but to permit the passage therethrough of air, said composite membrane disposed across said passageway, said passageway being intersected by said membrane and communicating with both the liquophilic and liquophobic components, said liquophilic and said liquophobic components being formed from the same material, the surface of at least one of said liquophilic and liquophobic components being permanently chemically modified.
2. A device according to claim 1 wherein the pore size of the liquophilic component of the membrane is from about 0.04 to about 0.65 μm .
3. A device according to claim 1 wherein the liquophilic component comprises from about 50 to about 70% of the gross surface area of the membrane.

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4. A device according to claim 1 wherein the volume between the composite membrane and the dropper tip orifice is from about 0.001 to about 0.15 cm³.
- 5 5. A device according to claim 1 wherein the liquophobic component has a critical wetting surface tension of less than about 35 dynes/cm.
- 10 6. A device according to claim 5 wherein the liquophilic component of the composite membrane has a critical wetting surface tension of at least about 72 dynes/cm.
7. A device according to claim 1 wherein the liquophilic component is made from a surface-modified microporous polyamide membrane.
- 15 8. A device according to claim 1 wherein said liquophobic component is made from a polyamide membrane surface-modified to have a critical wetting surface tension of less than about 28 dynes/cm.
- 20 9. A device according to claim 7 wherein said liquophobic component is made from a polyamide membrane surface-modified to have a critical wetting surface tension of less than about 28 dynes/cm.
- 25 10. A device according to claim 1 wherein said liquophobic component is made from polyvinylidene difluoride.

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11. A device according to claim 1 wherein said
liquophilic component comprises polyvinylidene
difluoride, surface-modified to render it
hydrophilic.

5 12. A device according to claim 10 wherein
said liquophilic component comprises polyvinylidene
difluoride, surface-modified to render it
hydrophilic.

10 13. A device according to claim 1 wherein said
liquophobic component comprises polyvinylidene
difluoride, surface-modified to have a critical
wetting surface tension of less than about 28
dynes/cm.

15 14. A device according to claim 11 wherein
said liquophobic component comprises polyvinylidene
difluoride, surface-modified to have a critical
wetting surface tension of less than about 28
dynes/cm.

20 15. A device according to claim 1 wherein the
container has elastically deformable sides and is
deformable by squeezing.

25 16. A device according to claim 1 wherein the
porosity of the microporous membrane is suitable for
resisting the passage of bacterial contamination and
the hydrophilic component has a gross surface area
of from about 20 mm² to about 90 mm².

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17. A device according to claim 1 wherein the CWST of said liquophilic component is at least about 72 dynes/cm and said liquophobic component is less than about 28 dynes/cm.

5 18. A device according to claim 1 wherein said orifice comprises a single orifice.

19. A device according to claim 1 wherein said liquophilic and liquophobic components are arranged in juxtaposed relationship.

10 20. A device according to claim 1 in which said composite microporous membrane has liquophilic and liquophobic components bonded together in side-by-side relationship, the liquophilic component having a surface area of from about 20 mm² to about
15 90 mm², an average pore size of from about 0.15 to about 0.25 μ m, and a CWST of at least about 72 dynes/cm; and the liquophobic component having a CWST of less than about 28 dynes/cm and having an average pore size of from about 0.1 to about 0.2 μ m.

20 21. A device according to claim 20 wherein said composite membrane comprises a polyamide.

22. A device according to claim 20 wherein said composite membrane comprises polyvinylidene difluoride.

25 23. A dispensing cap for use with a container for dispensing liquids in drop form, the cap comprising a dropper tip including a passageway for ingress of air to and egress of liquid from the container, said passageway communicating between the

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container and an orifice in the dropper tip; and a microporous composite membrane with pores of a size to resist passage of contaminants and having a liquophilic component permitting delivery of drops
5 of a liquid to a desired location outside the container and a liquophobic component adapted to resist the passage of such liquid but to permit the passage therethrough of air, said composite membrane disposed across said passageway, said passageway
10 being intersected by said membrane and communicating with both the liquophilic and liquophobic components, said liquophilic and said liquophobic components being formed from the same material, the surface of at least one of said liquophilic and
15 liquophobic components being permanently chemically modified.

24. A dispensing cap according to claim 23 wherein the pore size of the liquophilic component of the membrane is from about 0.04 to about 0.65 μm .

20 25. A dispensing cap according to claim 24 wherein the liquophilic component comprises from about 50 to about 70% of the gross surface area of the membrane.

25 26. A device according to claim 23 wherein the volume between the composite membrane and the dropper tip orifice is from about 0.001 to about 0.15 cm^3 .

30 27. A dispensing cap according to claim 23 wherein the liquophobic component has a critical wetting surface tension of less than about 35 dynes/cm.

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28. A dispensing cap according to claim 23 wherein the liquophilic component of the composite membrane has a critical wetting surface tension of at least about 72 dynes/cm.

5 29. A dispensing cap according to claim 23 wherein the liquophilic component is made from a surface-modified microporous polyamide membrane.

10 30. A dispensing cap according to claim 23 wherein said liquophobic component is made from a polyamide membrane surface-modified to have a critical wetting surface tension of less than about 28 dynes/cm.

15 31. A dispensing cap according to claim 29 wherein said liquophobic component is made from a polyamide membrane surface-modified to have a critical wetting surface tension of less than about 28 dynes/cm.

20 32. A dispensing cap according to claim 23 wherein said liquophobic component is made from polyvinylidene difluoride.

33. A dispensing cap according to claim 23 wherein said liquophilic component comprises polyvinylidene difluoride, surface-modified to render it hydrophilic.

25 34. A dispensing cap according to claim 32 wherein said liquophilic component comprises polyvinylidene difluoride, surface-modified to render it hydrophilic.

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35. A dispensing cap according to claim 23 wherein said liquophobic component comprises polyvinylidene difluoride, surface-modified to have a critical wetting surface tension of less than
5 about 28 dynes/cm.

36. A dispensing cap according to claim 33 wherein said liquophobic component comprises polyvinylidene difluoride, surface-modified to have a critical wetting surface tension of less than
10 about 28 dynes/cm.

37. A dispensing cap according to claim 23 wherein the porosity of the microporous membrane is suitable for resisting the passage of bacterial contamination and the hydrophilic component has a
15 gross surface area of from about 20 mm² to about 90 mm².

38. A dispensing cap according to claim 23 wherein the CWST of said liquophilic component is at least about 72 dynes/cm and said liquophobic
20 component is less than about 28 dynes/cm.

39. A dispensing cap according to claim 23 wherein said orifice comprises a single orifice.

40. A dispensing cap according to claim 23 wherein said liquophilic and liquophobic components
25 are arranged in juxtaposed relationship.

41. A dispensing cap according to claim 23 in which said composite microporous membrane has liquophilic and liquophobic components bonded together in side-by-side relationship, the

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liquophilic component having a surface area of from about 20 mm² to about 90 mm², an average pore size of from about 0.15 to about 0.25 μ m, and a CWST of at least about 72 dynes/cm; and the liquophobic
5 component having a CWST of less than about 28 dynes/cm and having an average pore size of from about 0.1 to about 0.2 μ m.

42. A device according to claim 41 wherein said composite membrane comprises a polyamide.

10 43. A device according to claim 41 wherein said composite membrane comprises polyvinylidene difluoride.

1/2

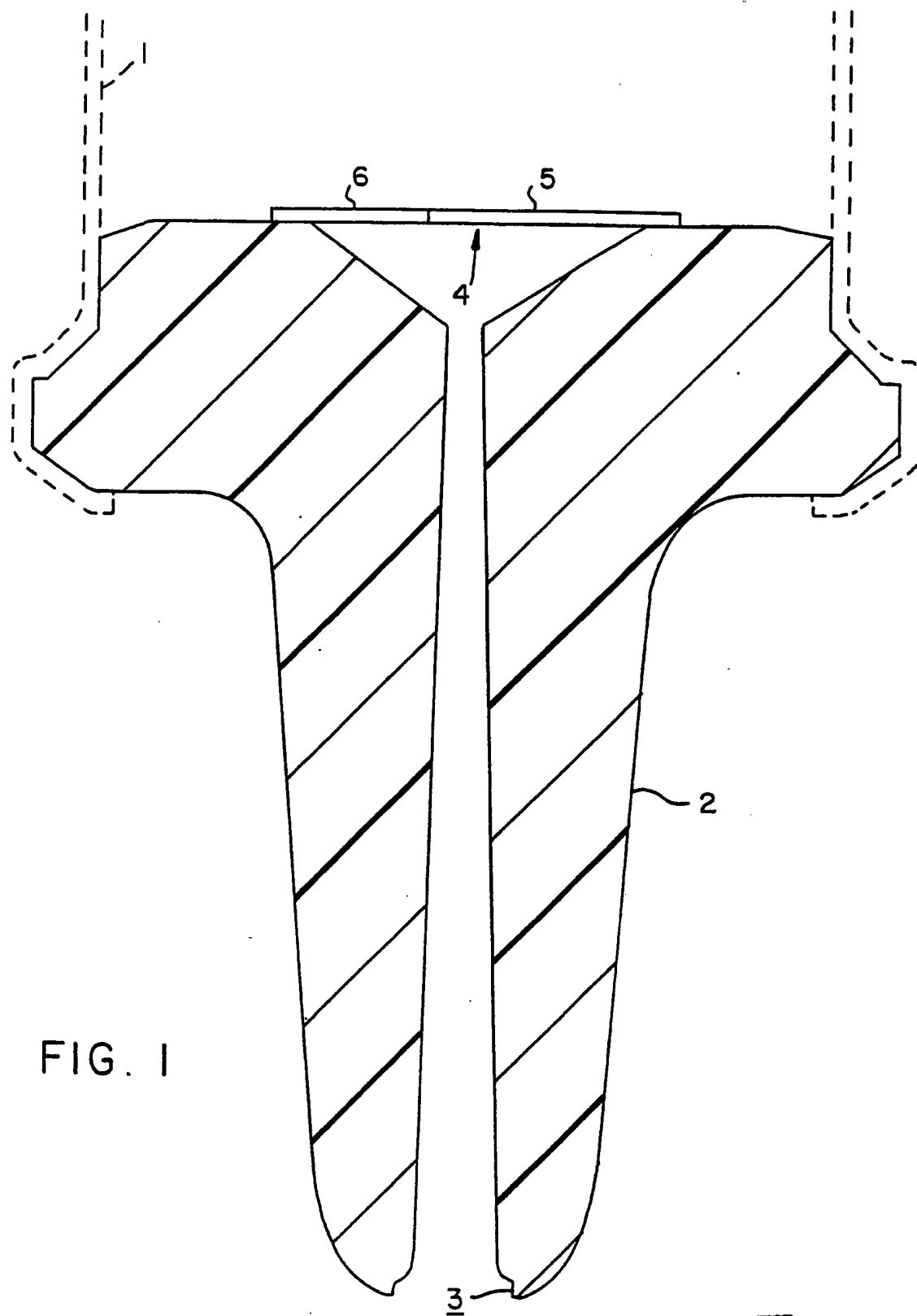
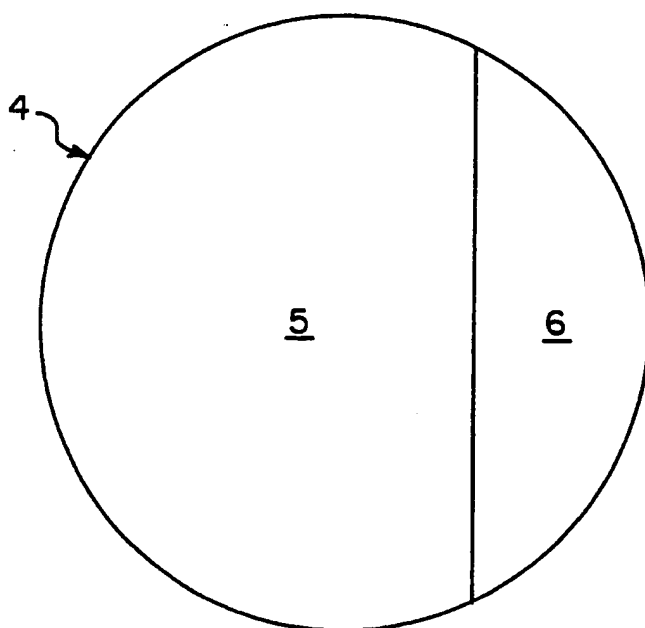


FIG. 1

SUBSTITUTE SHEET

FIG. 2



INTERNATIONAL SEARCH REPORT

International Application No. PCT/US90/07029

I. CLASSIFICATION OF SUBJECT MATTER

IPC(5): B67D-5/58

US CL.: 222/189

II. FIELDS SEARCHED

US 222/189,420
604/126,295,298
210/321.64,321.84,500.38,500.42

Documentation Search and Classification Manual on Documentation
to the Extent that such Documents are Included in the Search

III. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of Document, Title, Publication, Date of Publication, and Date of Filing	Relevance
X	US, A, 4,917,271 (KANNER et al.) 17 April 1990	1,15
Y	See column 1, lines 11-40.	2-14,16-43
Y	US, A, 4,915,839 (MARINACCIO et al.) 10 April 1990	7-9,21,29-31,42
Y	US, A, 4,319,996 (VINCENT et al.) 16 March 1982	20,23,41
Y	US, A, 4,203,848 (GRANDINE, II) 20 May 1980	10-14,22,32-36,43
A	US, A, ,4938,389 (ROSSI et al.) 03 July 1990	
A	US, A, 4,533,068 (MEIERHOEFER) 06 August 1985	
A	US, A, 4,463,880 (KRAMER et al.) 07 August 1984	
A	US, A, 4,002,168 (PETTERSON) 11 January 1977	
A	US, A, 3,149,758 (BUSH et al.) 22 September 1964	

* Special categories of cited documents: "C"

"A" document defining the general state of the art which is not considered to be of particular relevance

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application cited to understand the principle or theory underlying the invention

"X" document of particular relevance, the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search

Date of Mailing of this International Search Report

28 MARCH 1991

29 APR 1991

International Searching Authority

Signature of Authorized Officer

ISA/US

Boris Milef
BORIS MILEF